

Amendments to the claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of claims

Claim 1 (canceled)

Claim 2 (currently amended): A method for diagnosing disease in a female subject using an experimental sample derived from said subject comprising:
selecting reference samples of known disease state that ~~is~~ are matched to said experimental sample in reproductive state wherein the reproductive state of the individual is determined by determining at least one of the following parameters:

the menstrual state of the individual;

if the individual is post-partum;

if the individual is or has ever been pregnant;

if the individual is or has ever lactated;

if the individual is nulliparous;

comparing the expression profile of said experimental sample to the expression profiles of said reference samples to identify the reference sample that matches said experimental sample in gene expression; and

diagnosing the experimental sample with the disease of the matching reference sample.

Claim 3 (canceled)

Claim 4 (currently amended): A method to diagnose physiological disorders in a female comprising:

comparing a gene expression profile from an experimental sample to a gene expression profile that represents an average of a plurality of reference samples wherein all of the reference samples in the plurality share at least one indicator of reproductive status in common, wherein indicators of reproductive status are selected from the group

consisting of menstrual state, post-partum state, pregnancy state, lactation state and nulliparity state, and wherein each of the reference samples in the plurality have been diagnosed with the same physiological disorder and wherein the experimental sample also shares the at least one indicator of reproductive status with matching indicators of reproductive status; and

diagnosing the experimental sample with the physiological disorder if the gene expression profile of the experimental sample is similar to the gene expression profile that represents an average of a plurality of reference samples using said profile information to diagnose physiological disorders.

Claim 5 (currently amended): A method to identify the reproductive status of a sample derived from a female comprising:
generating an expression profile from the experimental sample, and comparing said expression profile from the experimental sample to a plurality of expression profiles from samples of known reproductive ~~state~~ status, wherein the reproductive state of the individual is determined by determining at least one of the following parameters:

the menstrual state of the individual;

if the individual is post-partum;

if the individual is or has ever been pregnant;

if the individual is or has ever lactated;

if the individual is nulliparous; and

identifying said ~~physiological~~ reproductive status of said sample of unknown origin ~~using said expression profile~~ by identifying an expression profile of determined reproductive status that is similar to the expression profile from the experimental sample.

Claim 6 (currently amended): A method to identify markers of different reproductive states in women comprising:

obtaining a first gene expression profile ~~matching from~~ a sample from a first physiological reproductive state and a second gene expression profile from ~~to~~ a sample

from a second ~~physiological~~ reproductive state, wherein the reproductive state of the individual is determined by determining at least one of the following parameters:

the menstrual state of the individual;

if the individual is post-partum;

if the individual is or has ever been pregnant;

if the individual is or has ever lactated;

if the individual is nulliparous;

comparing the expression profiles from said first and second ~~physiological~~ reproductive states;

identifying genes that are differentially expressed in said first and second reproductive states; and

~~using the~~ identifying at least one gene that is differentially expressed between the first and second reproductive states as a marker ~~expression profile data to identify markers~~ of different ~~physiological~~ reproductive states in women ~~humans~~.

Claims 7-9 (canceled)

REMARKS/ARGUMENTS

The Office Action mailed April 28, 2003 and the Advisory Action mailed August 25, 2003 have been carefully reviewed and the foregoing amendments are made in response thereto. In view of the amendments and the following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Applicants have cancelled claims 7-9 without prejudice. Applicants have amended claims 2, and 4-6 for the purpose of expediting the issuance of claims. Claim 2 has been amended to correct grammatical errors. In addition claim 2 has been amended to clarify that the subject being diagnosed by comparison to samples of matched reproductive state is female. Support for this amendment may be found throughout the specification and particularly at page 23, lines 25-26. Claims 4 and 5 have been similarly amended to clarify that the experimental sample is from a female.

Claim 4 has been amended to clarify that the reference samples that are used to generate the average expression profile are matched in at least one indicator of reproductive status and to clarify that the experimental sample is diagnosed with a physiological disorder by comparing the gene expression profile to an average gene expression profile. Support for the amendments may be found throughout the specification, for example on page 15, lines 27-30. The specification also teaches that an experimental sample is compared to reference samples of known disease states and the experimental sample is diagnosed with the disease of the matching reference sample(s) (page 18, lines 3-9).

Claim 5 has been amended to clarify that it is a method to identify the reproductive status as indicated in the preamble. In addition the claim has been amended to recite a final process step that clearly relates back to the preamble. Specifically the phrase "using said expression profile" has been replaced with the phrase "by identifying an expression profile of known reproductive status that is similar to the expression profile from the experimental sample." The methods of the invention generally involve comparing gene expression profiles from experimental samples to gene expression profiles from samples of known status to identify the status of the experimental sample

by identifying a similar sample of known status. In claim 5 it is the reproductive status that is being determined.

Claim 6 has been amended to clarify that gene expression profiles are obtained from different reproductive states and compared to identify genes that are differentially expressed between the two states. The final step has been amended to clarify that the markers identified are of different reproductive states in women.

Claims 2, and 4-6 have been amended to add the limitation that reproductive status be determined by determining at least one of a limited number of parameters. The parameters are menstrual state, post-partum state, pregnancy state, lactation state and nulliparity state. Support for these amendments may be found in the specification at page 5, lines 24-27.

It is respectfully submitted that no new matter has been introduced by the present amendments and entry of the same is respectfully requested. Applicants respectfully request reconsideration of the pending rejection and reexamination of the present claims in light of the amendments and the remarks detailed below.

By these amendments, the Applicants do not acquiesce to the propriety of any of the Examiner's rejections and do not disclaim any subject matter to which Applicants are entitled.

35 U.S.C. § 112 Rejection

In Paragraph 3A) of the office action the examiner has rejected claims 2 and 4-9 under 35 U.S.C. 112, second paragraph as being indefinite because "it is uncertain as to what encompasses 'reproductive state'" Applicants respectfully disagree. One of skill in the art would understand that reproductive state entails parameters that are related to the normal variations in reproductive events. This includes whether or not a woman is or has ever been pregnant and if so, how many pregnancies and the outcome of those pregnancies, whether a woman has lactated and if so for how long, whether a woman is pre-menopausal, peri-menopausal, menopausal or post-menopausal and what phase of the menstrual cycle the individual was in when the sample was isolated. In an effort to expedite issuance of the pending claims, Applicants have amended claims 2 and 4-6 to

add the limitation that reproductive state be determined by determining at least one of a limited set of parameters. These parameters are menstrual state, post-partum state, pregnancy state, lactation state and nulliparity state.

In Paragraph 3B) the Examiner indicates that “reproductive state” and “reproductive status” are not defined in the specification. As indicated above Applicants believe that it would be clear to one of skill in the art what parameters would be included in determining reproductive state, but Applicants have amended the claims as indicated above to more clearly define the claimed subject matter.

Claims 7-9 have been canceled making the rejection of these claims in paragraph 3C) moot. Claim 6 is not dependent on claim 5.

Claims 5 and 6 have been amended to recite a final process step which clearly relates back to the preamble as suggested in paragraph 3D).

Anticipation Rejection Under 35 U.S.C. § 102(e)

The Examiner has rejected claims 2 and 4-6 under 35 U.S.C. 102(e) as being anticipated by Friend *et. al.*, (US 6,218,122). Applicants respectfully traverse this rejection.

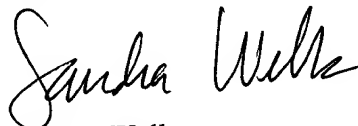
Applicants have amended the claims to remove ambiguity in the terms “reproductive state” and “reproductive status”. Matching samples simply by sex or age is not identical to matching samples according to at least one of the claimed parameters of reproductive status. Matching the reproductive status of samples presupposes that the samples are from females and requires at least one additional matching parameter that reflects reproductive state as claimed. Applicants respectfully submit that Friend *et. al.* does not disclose comparing gene expression of samples with matching reproductive state. Therefore, the rejection under 102(e) should be withdrawn.

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Amdt. Dated September 29, 2003
Reply to Office Action of April 28, 2003

CONCLUSION

For these reasons, Applicants believe all pending claims are now in condition for allowance and should be passed to issue. If the Examiner feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at (408) 731-5768. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account 01-0431.

Respectfully submitted,



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Date: 9/29/2003
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